



PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional)
OMRF 128 CON

In re Application of Philip C. Comp

Application Number 08/323,060

Filed 10/14/1994

For Blockage of Protein C Activation Reduces Microvascular
Surgical Blood Loss

Group Art Unit 1644

Examiner
Ronald B. Schwadron

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows
(check time period desired):

☒ One month (37 CFR 1.17(a)(1))

\$ 110.00

☐ Two months (37 CFR 1.17(a)(2))

\$

☐ Three months (37 CFR 1.17(a)(3))

\$

☐ Four months (37 CFR 1.17(a)(4))

\$

☐ Five months (37 CFR 1.17(a)(5))

\$

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ 55.00

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1868

I have enclosed a duplicate copy of this sheet.

I am the ☐ assignee of record of the entire interest.

☐ applicant.

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a).

Registration number if acting under 37 CFR 1.34(a)

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July 17, 2003

Date

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Patrea L. Pabst, Reg. No. 31,284

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/323,060
Filing Date	October 14, 1994
First Named Inventor	Philip C. Comp
Art Unit	1644
Examiner Name	Ronald B. Schwadron
Attorney Docket Number	OMRF 128 CON

Total Number of Pages in This Submission

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual	Patrea L. Pabst, Esq., Reg. No. 31,284 Suite 2000, One Atlantic Center; 1201 West Peachtree Street, N.E.; Atlanta, GA 30309-3400	Holland & Knight LLP
Signature		
Date	July 17, 2003	

CERTIFICATE OF TRANSMISSION/MAILING

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Signature		Date	July 17, 2003

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) 215.00

Complete if Known

Application Number 08/323,060
Filing Date October 14, 1994
First Named Inventor Philip C. Comp
Examiner Name Ronald B. Schwadron
Art Unit 1644
Attorney Docket No. OMRF 128 CON

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METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

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50-1868

Holland & Knight LLP

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☒ Charge fee(s) indicated below ☒ Credit any overpayments
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 750	2001 375	Utility filing fee	
1002 330	2002 165	Design filing fee	
1003 520	2003 260	Plant filing fee	
1004 750	2004 375	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	

SUBTOTAL (1) (\$)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims	Extra Claims	Fee from below	Fee Paid
15	-20	0	0
1	-3**	0	0
Multiple Dependent			

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
1202 18	2202 9	Claims in excess of 20
1201 84	2201 42	Independent claims in excess of 3
1203 280	2203 140	Multiple dependent claim, if not paid
1204 84	2204 42	** Reissue independent claims over original patent
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$) 0.00

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	55.00
1251 110	2251 55	Extension for reply within first month	
1252 410	2252 205	Extension for reply within second month	
1253 930	2253 465	Extension for reply within third month	
1254 1,450	2254 725	Extension for reply within fourth month	
1255 1,970	2255 985	Extension for reply within fifth month	
1401 320	2401 160	Notice of Appeal	160.00
1402 320	2402 160	Filing a brief in support of an appeal	
1403 280	2403 140	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,300	2453 650	Petition to revive - unintentional	
1501 1,300	2501 650	Utility issue fee (or reissue)	
1502 470	2502 235	Design issue fee	
1503 630	2503 315	Plant issue fee	
1460 130	1460 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1806 180	1806 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 750	2809 375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 750	2810 375	For each additional invention to be examined (37 CFR 1.129(b))	
1801 750	2801 375	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$) 215.00

SUBMITTED BY

(Complete if applicable)

Name (Print/Type)	Patrea L. Pabst	Registration No. (Attorney/Agent)	31,284	Telephone (404) 817-8473
Signature		Date	July 17, 2003	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant: Philip C. Comp

Serial No.: 08/323,060

Art Unit: 1644

Filed: October 14, 1994

Examiner: Ronald B. Schwadron

For: *"BLOCKAGE OF PROTEIN C ACTIVATION REDUCES MICROVASCULAR
SURGICAL BLOOD LOSS"*

Mail Stop Appeal Brief-Patents
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Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims in the Office Action mailed December 13, 2002, in the above-identified patent application. A Notice of Appeal was mailed on April 17, 2003. A Petition for an Extension of Time for One Month is enclosed. The Commissioner is hereby authorized to charge \$160.00 the fee for filing of this Appeal Brief (small entity), and \$55.00 for the Petition for an Extension of Time for One Month, to extend the response one month, up to and including July 17, 2003, to the Deposit Account No. 50-1868.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Oklahoma Medical Research Foundation, Oklahoma City, OK, the assignee.

(2) RELATED APPEALS AND INTERFERENCES

This case was previously on Appeal before the Board of Patent Appeals and Interferences (Appeal No. 1999-2254). In the Decision, the Board affirmed the rejection of claims 14-16 under 35 U.S.C. § 112, first and second paragraphs. The Board reversed all other rejections as they applied to claims 1-9, 11-13 and 19-21.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-9, 11-13, and 19-21 are pending and on appeal. Claims 10 and 14-18 were previously canceled as described in the Appendix to this Brief. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An amendment after final rejection was mailed on March 13, 2003. In the Advisory Action mailed on March 27, 2003, the Examiner indicated that the after final amendment was non-responsive under 37 C.F.R. 1.121 and would not be entered. The appellants mailed a corrected version of the after final amendment on April 17, 2003. In phone call with the Appellant's representative on July 15, 2003, the Examiner stated that he had **not** yet reviewed the amendment filed on April 17, 2003. Therefore, **no indication has been made as to whether the after final amendments, as submitted on April 17, 2003, will be entered.** An appendix sets forth the claims on appeal.

(5) SUMMARY OF THE INVENTION

The presently claimed invention is a method for inhibiting microvascular bleeding at a site in a patient by administering to the patient a compound in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of protein C, antithrombin III, heparin cofactor II, thrombomodulin or tissue factor pathway inhibitor (see page 14, lines 21-27). The inhibitor may be administered systemically or topically (see page 14, lines 12-17). One may additionally administer a coagulant topically to the site of the bleeding (see page 14, lines 13-15). The coagulant may be thrombin or tissue thromboplastin (see page 13, lines 6-16 and lines 27-30). The inhibitor may be an antibody to protein C (see page 18, lines 18-31). The inhibitor may be administered systemically and a coagulant administered topically at the site of bleeding (page 14, lines 13-15). The topically administered coagulant may be thrombin in a dosage of between approximately 1000 and 10,000 units or tissue factor in a dosage of between approximately 0.1 and 10 mg (see page 16, lines 25-27). The inhibitor may be administered to a burn patient, a patient with tissue or skin grafts, or a patient with cerebral contusions (see page 14, lines 1-3; and lines 8-11). The inhibitor may be a monoclonal antibody that is immunoreactive with protein C and blocks protein C activation (see page 18, lines 13-21) such as HPC-4 (see page 12, lines 9-29; page 14, lines 21-27; and page 18, lines 13-21).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

- (1) whether claims 1-6, 11-13, and 19 meet the written description requirement as required by 35 U.S.C. § 112, first paragraph; and
- (2) whether claims 7-9, 20 and 21 were properly rejected objected to as being dependent upon a rejected base claim (this rejection would be mooted if the amendment after final is entered).

(7) GROUPING OF CLAIMS

Claims 1-6, 11-3, and 19 stand or fall together with respect to the single basis on which the claims have been rejected as not in compliance with the written description requirement under 35 U.S.C. 112, for not being limited to an antibody.

(8) ARGUMENTS

(a) The Claimed Invention

The claims define a method for reducing blood loss from microvascular bleeding due to wounds caused by surgery or trauma, in particular bleeding from skin graft donor sites, burns, bleeding liver surfaces, and inflamed visceral surfaces. These types of injuries are particularly difficult to treat. Burns, for example, may cover a large surface area and ooze for days due to the massive inflammation and loss of epidermal cover. Liver is highly vascularized and if cut to remove a tumor or during transplant, may bleed for extended periods of time. Unlike a more typical cut or wound, microvascular bleeding is extremely difficult to control. The prior art method of treatment typically consisted of topical administration of thrombin, which sometimes worked, but often had little efficacy.

Appellant, Dr. Comp, is a medical doctor and researcher in the field of blood clotting disorders and the components involved in this process. In the late 1980's, he and Dr. Charles Esmon discovered that an inhibitor of a natural anticoagulant, protein C, could be used to kill tumors. They used a monoclonal antibody immunoreactive to protein C, but not the "activated" form of protein C, referred to as HPC-4, in their studies in a variety of animal species having a number of different solid tumors to demonstrate efficacy. This discovery formed the basis of a patent application which issued with claims to methods and compositions for inhibition of tumors in 1992 as U.S. Patent No. 5,147,638 to Charles Esmon and Philip Comp. An earlier filed application issued with claims to the HPC-4 antibody in 1993 as U.S. Patent No. 5,202,253 to Charles and Naomi Esmon.

The method for treating tumors was enhanced by the use of a cytokine, such as tumor necrosis factor, and was thought to kill the tumors by causing massive microvascular clotting within the tumors but not in normal tissue. It was not known why the systemic or local administration of the inhibitor, alone or in combination with a cytokine, did not cause clotting to occur in tissues other than the tumors, however, extensive autopsies showed the results were consistent in all animal models tested, including dogs, cats, pigs, and baboon.

Dr. Comp subsequently determined that systemic administration of an inhibitor of a natural anticoagulant, such as protein C, could also be used to inhibit microvascular bleeding in normal patients. This is typical of injuries such as in burn and skin graft patients, where large areas "ooze" fluids, causing extensive fluid loss, and pain due to adhesion to bandages, as well as

serving as entry sites for infection. It also occurs in brain trauma patients, where it is extremely difficult to treat without the risk of a clot forming and causing a stroke.

Dr. Comp conducted his experiments in pigs, removing areas of skin grafts (0.015 inches in thickness, application page 17). He treated the injured tissue with either (1) systemic HPC4; (2) systemic HPC4 with topical thrombin; (3) systemic HPC4 with topical thromboplastin; (4) saline control; (5) topical thrombin (prior art treatment); topical thromboplastin (application page 18). The analysis of the various treatments showed that systemic HPC4 was generally equivalent to the results obtained with topical thrombin or tissue thromboplastin, demonstrating the efficacy of systemic treatment of microvascular bleeding using an inhibitor of a natural anticoagulant. The analysis also demonstrated that the combination of systemic inhibitor with topical coagulant achieved a **33 to 44% decrease in blood loss** ($p < 0.05$) as compared with either systemic administration of inhibitor alone or topical thrombin alone (page 20, Figures 2 and 3).

The claimed methods define the use of an inhibitor of one or more natural anticoagulants: protein C, thrombomodulin, antithrombin II, heparin cofactor II or tissue factor pathway inhibitor, in an amount effective to prevent anticoagulation.

As is clear from the attached diagram of the clotting cascade, clotting components added in concert - not alone. This diagram shows protein C as "PC"; activated protein C as "APC", and thrombomodulin as "TM", and how these interact, so that inhibition at any point will inhibit anticoagulation - and allow clotting to occur. Although not shown in this diagram, antithrombin III, heparin cofactor II, and tissue factor pathway inhibitor play the same type of roles in

anticoagulation, so that inhibition of any of these molecules will also block the protein C anticoagulation pathway.

At the time of filing the present application, components of the coagulation pathway were known. Antibodies to protein C and inhibitors of the other components of the coagulation process were also known. The board previously acknowledged this when they found appellant's composition claims unpatentable.

However, the issue on appeal is not enablement or prior art but whether or not the disclosure of known materials in the application, along with actual reduction to practice of one embodiment of the claimed method, meets the written description requirement under 35 U.S.C. 112.

(b) Rejections Under 35 U.S.C. § 112

i. The Legal Standard for Written Description

As the Court of Appeals for the Federal Circuit recently stated in Amgen v. Hoechst, et al. 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003),

"the purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561, 19 USPQ2d 111, 1115 (Fed. Cir. 1991). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the

art to recognize that [the inventor] invented what is claimed.”). “Compliance with the written description requirement is essentially a fact-based inquiry that will ‘necessarily vary depending on the nature of the invention claimed.’” Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted)."

The Court of Appeal for the Federal Circuit's decision in Eli Lilly v. Univ. of Calif. Board of Regents In Regents of University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998) is not applicable in this case. The claims in this case are not drawn to claims to a protein or a gene encoding a protein, but to a method of use of known materials. In Enzo Biochem, the Federal Circuit held that that the written description requirement can be met by a functional description of *claimed materials*, if coupled with a known or disclosed correlation between function and structure. Enzo Biochem, Inc., v. Gen-Probe, Inc., 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo IP*"). Enzo is also not applicable in this case, again since appellant is claiming a method of using known materials, not the materials themselves.

In Amgen, the Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. § 112, stating

"Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." Reiterating, the Court stated that the standard was merely that "the patent specification must contain "a written description of the invention, and of the manner and

process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... ” "The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention."

ii. Rejection of Claims 1-6, 11-13 and 19 under 35 U.S.C. § 112, first paragraph

The specification clearly discloses the proteins to be inhibited (anticoagulants) and types of inhibitors such as antibodies; there has been no argument in this respect. The specification also states that other types of inhibitors can be used (bottom of page 12 to top of page 13).

The basis for the rejection is the Examiner's assertion that the only inhibitor of an anticoagulant disclosed in the specification is an antibody which binds the anticoagulant recited in the claims. The appellant respectfully submits that antibodies to the other proteins/anticoagulants were also known and available at the time of filing the present application. Evidence, in the form previously submitted references (see those submitted with the Office Action mailed on September 23, 2002), clearly showed that the activity of the anticoagulants recited in the claims could be inhibited by proteins and/or DNA oligonucleotides (see, for example, *J. Histochem. Cytochem.*, 1994 (10):1365-1376 [**anti-thrombin III antibody**]; *Hybridoma*, 1991(5):633-640 [**anti-thrombin III antibody**]; *J. Heart Lung Transplant.* 1992(2 pt. 1):342-347 [**anti-thrombin III antibody**]; *J. Histochem. Cytochem.*, 1994(10):1365-1376 [**anti-thrombin III antibody**]; *J. Chromatography*, 1991(2):493-500 [**heparin cofactor II antiserum**]; *Thromb. Haemost* 1992(5):507-509 [**thrombomodulin antibodies**]; *Kidney Int.*, 1992(5):1170-1174 [**thrombomodulin antibodies**]; and *Thromb. Haemost.*, 1992(3):310-314

[**tissue factor pathway inhibitor antibody**]). However, as demonstrated by the enclosed abstracts, other inhibitors of clotting protein were known and could therefore be used in the claimed method (see, for example, *Gene*, 1993, 137(1):25-31 [**inhibition of thrombin via single stranded DNA oligonucleotides**] in combination with *Seminars in Hematology*, Vol. 29 (3):159-169, 1992).

The examiner has apparently refused to consider these references on the ground that they were not recited in the specification. However, that is not the test. Appellant has demonstrated that the materials were known to those skilled in the art as of the effective filing date. Appellant has pointed to where in the specification one is told to use inhibitors of these anticoagulants, not just antibodies, not just to protein C. Therefore, one skilled in the art would not only be enabled, but the written description in the application as filed would be sufficient to describe to one skilled in the art what the invention is, in full compliance with 35 U.S.C. 112.

(c) Objections

Claims 7-9, 20 and 21 were objected to as being dependent upon a rejected base claim. The claims were amended to be in independent form in the after final response mailed on April 17, 2003. **There has been no indication as to whether the after final amendments, as submitted on April 17, 2003, will be entered.** The requested entry of the amendments were made to facilitate appeal.

(9) SUMMARY AND CONCLUSION

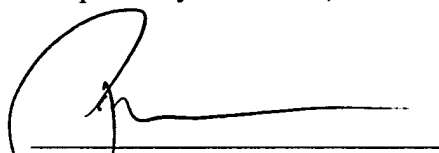
Since the compounds required by the claimed method were known as of the time of filing, and are recited in the application as filed, even if not actually reduced to practice, in a way

U.S.S.N. 08/323,060
Filed: October 14, 1994
APPEAL BRIEF

that one of ordinary skill in the art would be able to make and use the claimed method, all claims are in compliance with the written description requirement under 35 U.S.C. 112.

For the foregoing reasons, Appellant submits that the claims 1-9, 11-13, and 19-21 are patentable.

Respectfully submitted,




Patrea L. Pabst
Reg. No. 31,284

Date: July 17, 2003

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Patrea Pabst

Date: July 17, 2003

Appendix: Claims On Appeal

1. (three times amended) A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

2. (once amended) The method of claim 1 wherein the anticoagulant is protein C.

3. (once amended) The method of claim 1 wherein the inhibitor is administered systemically.

4. (original) The method of claim 1 wherein the inhibitor is administered topically.

5. (once amended) The method of claim 1 further comprising topically administering at the site of the bleeding a coagulant.

6. The method of claim 5 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

7. (once amended) The method of claim 2 wherein the inhibitor is an antibody to protein C.

8. (two times amended) The method of claim 7 wherein the inhibitor is administered systemically further comprising the step of topically administering a coagulant at the site of bleeding.

9. (original) The method of claim 8 wherein the topically administered coagulant is selected from the group consisting of thrombin in a dosage of between approximately 1000 and 10,000 units and tissue factor in a dosage of between approximately 0.1 and 10 mg.

11. (once amended) The method of claim 1 wherein the inhibitor is administered to a burn patient.

12. (once amended) The method of claim 1 wherein the inhibitor is administered to a patient with tissue or skin grafts.

13. (once amended) The method of claim 1 wherein the inhibitor is administered to a patient with cerebral contusions.

19. (original) The method of claim 4 further comprising the step of topically administering a coagulant at the site of bleeding.

20. (original) The method of claim 3 wherein the inhibitor is a monoclonal antibody immunoreactive with protein C and blocking protein C activation.

21. (original) The method of claim 20 wherein the inhibitor is HPC-4, deposited with the American Type Culture Collection, Rockville, MD and assigned ATCC No. 9892.

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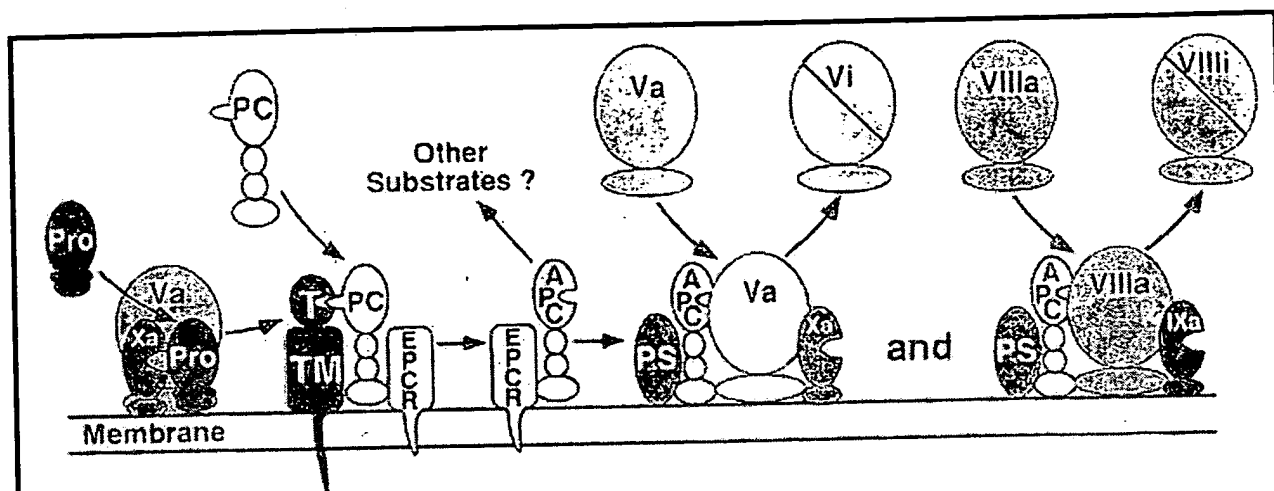


Figure 1. Model of the function of the protein C anticoagulant pathway. Thrombin (T) is generated from prothrombin (Pro) by the factor Va-factor Xa complex. T then binds to thrombomodulin (TM) to form the protein C activation complex. Protein C binds to the endothelial cell protein C receptor (EPCR), if present, and this complex is activated by the T/TM complex. Activated protein C (APC) can remain bound to EPCR, but this complex does not appear to be capable of inactivating factor Va, presumably an indication that it is targeted to as yet unidentified alternative substrates. When APC dissociates from EPCR, it can then bind to protein S (PS). This complex inactivates factor Va or factor VIIIa, thereby shutting down T formation and preventing blood clot extension. (Modified figure reprinted with permission from Stearns-Kurosawa DJ, Kurosawa S, Mollica JS, Ferrell GL, Esmon CT. The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex. *Proc Natl Acad Sci U S A* 1996;93:10212-10216; Esmon CT. The protein C anticoagulant pathway. *Arterioscler Thromb Vasc Biol* 1992;12:135-145.)³

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